Guidelines for Completing Case Report Forms For A Six-Week Randomized Double-Blind, Controlled Trial of High Dose Asacol (6.0 g/day) Versus Low Dose Asacol (2.4 or 3.6 g/day) for the Treatment of Mild to Moderate Crohn's Disease

Version 4
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Table of Contents

1.0 Contact List

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Note: For Federal Express & Mail, please address to Dr. James Marion, Attn: Reina Nakamura

Mayo Clinic Study Coordinator
Resa Jeche or Therese Johnson, RN
IBD Clinical Research Unit
Mayo Building, E19B - Room 1939
200 First Street SW
Rochester, MN 55905

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2.0 QUICK REFERENCE GUIDE

Randomization//Serious Adverse Events/Case Report Forms

James F. Marion, MD
Attention: Reina Nakamura
12 East 86th Street
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Attention: Resa Jeche E19B Room 1939
200 First Street SW
Rochester MN 55905
Phone: 507-284-5908 or 507-255-3328
Fax: 507-284-3923
E-mail: jeche.resa@mayo.edu

2.1. Randomization

To randomize a patient you must fax and mail the Inclusion/Exclusion Criteria to Reina and fax it to Resa.

2.2. Serious Adverse Events

All Serious Adverse Events should be reported immediately by fax to both Reina and Resa followed up by mail to Reina.

2.3. Case Report Forms/Patient Diaries

All CRFs (the white and yellow copies) should be mailed to Reina within 2 weeks of a completed visit. Address:
Dr. James Marion
Attn: Reina Nakamura
12 East 86th Street
New York, NY 10028-0506

2.4. Adverse Events/Concomitant Medication/Study Termination Forms

These completed forms should be mailed to Reina within 2 weeks of the patient's completion or Termination of the study.

3.0 Introduction

These instructions were designed to assist site study coordinators in completing and submitting the case report forms. Much of the success of the study depends on how well you are able to capture and record the necessary data. Please do not hesitate to contact the Study Coordinator when questions arise. A newsletter will be published periodically that will help answer questions and provide clarifications.

Please refer to each Visit Forms Checklist and Table A: Schedule of Events (attached) from the protocol for the required case report forms that need to be completed at each visit.

3.1 Specific Aims of this Trial

The objective of this trial is to evaluate the safety and efficacy of Asacol 6.0 g/day versus Asacol 2.4 g/day for 6 weeks in patients with mildly to moderately active Crohn's Disease. A secondary objective is to assess the impact of Asacol 6.0 g/day versus Asacol 2.4 g/day on the quality of life in the patients.

4.0 Enrollment: Site Responsibilities

4.1 Inclusion/Exclusion Criteria

A patient is only eligible for this study when all inclusion/exclusion criteria are met. This can be found on the Inclusion/Exclusion Criteria Form at the Baseline Visit.

Under certain circumstances, a deviation from these criteria may be allowed but must be approved by both the Principal Investigator and the Mayo Clinic.

4.2 Submitting Inclusion/Exclusion Form

A copy of the Inclusion/Exclusion Form **MUST BE FAXED** to the Mayo Clinic Study Coordinator and Reina Nakamura **WITHIN 24 HOURS** of the patient's enrollment in the study. Please fax Inclusion/Exclusion form to:

Resa Jeche
IBD Clinical Research Unit
Mayo Building, E19B - Room 1939
FAX #: 507-284-3923

And

Reina Nakamura

FAX #: 212-628-3648

5.0 Randomization and Assignment of Patient Numbers

5.1 Randomization

Patients meeting eligibility requirements will be randomized to receive either Asacol 2.4g/day or Asacol 6.0 g/day. The randomization scheme will be accomplished using random numbers, assigning each participant to one of the two groups.

5.2 Assignment of Patient Numbers

Each site has a unique identification code and each patient will be assigned a unique number within that site. The patient number will be 5 numeric digits (with the first 2 numbers being the site number). Resa Jeche, the Study Coordinator at the Mayo Clinic, will assign the numbers and keep the master lists.

5.3 Patients that are Screened but not Randomized

A Master Patient Log of all patients screened must be also be maintained. Site coordinators should send the Screening, Baseline, and Early Termination forms for the patients who fail screening. On the Study Termination form, Number 8 –Failed Screening Criteria -should be circled and the reason should be written in the space.

6.0 Data Handling Procedures

6.1 Questions Concerning Clinical or Data Recording Issues

Any questions pertaining to clinical data (i.e., meeting the inclusion / exclusion criteria, data recording, discrepancy clarification, etc.) should be directed to the Study Coordinator, Reina Nakamura by phone (212-249-1039) or by e-mail (reina.nakamura@ibdresearch.com)

6.2 Recording Study Data

General Instructions for completing the case report forms:

- All Case Report Forms must be completed with a black ballpoint.
- All Case Report Forms must be completed with clear legible print. All ineligible writing will generate a query and the form will not be considered complete until the query is resolved.
- Answer each question and fill in each blank, unless there is a skip pattern (i.e. Go to Quest #). Any form that is not completely filled out will be considered incomplete and will be returned to the site for completion.

6.3 Correcting Study Data

- If there is an error on a form that needs correction, strike through the incorrect data with one line, initial and date the change. Print the corrected data in the margin.

6.4 Submitting Study Data

The original top white form and 2nd yellow copy of all CRFs (with the exception of the Informed Consent) must be submitted to the Study Coordinator within 2 weeks of the patient's visit. It is essential for study data to be collected and recorded in a timely manner. All forms submissions will be tracked by the Data Management Center and any forms that are not received in a timely manner will result in a query to the site.

Send data via regular mail to:

James F. Marion, MD
Attn: Reina Nakamura
12 East 86th Street
New York, NY 10028-0506

7.0 Other Procedures

7.1 Visit Schedule

Once a patient's Inclusion/Exclusion and Informed Consent data has been confirmed by the Mayo Center Study Coordinator, the Study Coordinator will return Confirmation of Enrollment and a Visit Schedule for that particular patient. All efforts should be made to keep patient's visits within the Visit Schedule windows. If a patient does not keep the visit in the time allowed, the visit will be considered missed.

7.2 Missed or Skipped Visits

If a visit is not made within the appropriate visit window, complete the appropriate Visit Forms Checklist and submit the blank corresponding case report forms for that visit.

7.3 Unscheduled or Extra Visit

- If the patient has an appointment at any other time than the designated VISIT SCHEDULE, that visit will be reported as an UNSCHEDULED VISIT, go to the Unscheduled Visit tab and complete the appropriate forms.
- If a patient happens to have 2 appointments within one visit window, the first visit will be considered the scheduled visit and the second visit will be considered an Unscheduled Visit.

7.4 Discontinued Patients

If the patient terminates the study early, that visit will be reported as an EARLY TERMINATION VISIT, go to the Early Termination Visit tab and complete the appropriate forms.

8.0 Case Report Forms: Instructions for Completion

VERY IMPORTANT: Answer each question and fill in each blank, unless there is a skip pattern (i.e. Go to Quest #). Any form that is not completely filled out will be considered incomplete and will be returned to the site for completion.

8.1 Visit Forms Checklist (All Visits)

Each visit has a forms checklist to complete and submit. Please record the date of the patient's visit. Circle one number: 1 (yes), 2 (no), or 3 (na) and record the date sent for each of the required and if applicable forms. If a form is not sent, explain why.

8.2 Patient Description (Screening Visit)

Record the patient's date of birth and current age at the time of visit. Circle the number for ethnic group and sex. If a patient's ethnic group does not fit in the listed categories, circle 5 (other) and specify the other in the blank.

8.3 Crohn's Medical History (Screening Visit)

Page 1:
Criteria for Crohn's disease diagnosis: circle 1 (yes), 2 (no) or 3 (don't know) for clinical, colonoscopy, small bowel, and histology. If 1 is circled for yes, also complete the date of diagnosis (month and year).

Note: If none of the criteria are answered yes, the patient does not qualify for the study. Complete a Study Termination Form in the Early Termination Visit tab and discontinue screening.

Localization of Crohn's disease: Circle 1 (ileum only), 2 (colon only), or 3 (ileocolonic). Note: Choose only one.

Resection: Circle 1 (yes) or 2 (no). If 2 (no) is circled, skip to Question 5.

If 1 (yes) is circled, record the number of previous resections and month and year of the most recent.

Record the number of flares in the past two years.

Record the number of Crohn's related hospitalizations in the past two years.

Page 2:
Complications verified: circle 0 (never a problem), 1 (previous problem), 2 (current problem) or 3 (don't know) for each of the complications listed.

Note: If 2 (current problem) is circled for abscess or obstruction, the patient does not qualify for the study. Complete a Study Termination Form in the Early Termination Visit tab.

Extra-intestinal manifestations of Crohn's disease: circle 0 (never a problem), 1 (previous problem), 2 (current problem) or 3 (don't know) for each of the manifestations listed.

Note: If 2 (current problem) is circled for any of the manifestations, be sure to also record on the Comprehensive Physical Exam Form. Failure to do so will generate a query when the data is entered.

8.4 Comprehensive Physical Exam (Screening Visit)

Record weight (indicating kg or lb by checking the box), height (checking in or cm), temperature (checking °F or °C), pulse rate, and systolic and diastolic BP. Also answer yes or no for blood and urine samples sent to Lab.

Circle either 1 (normal) or 2 (abnormal) for each of the Physical Exam Items. If 2 (abnormal) is circled for any items, specify the abnormality.

Answer 1 (yes) or 2 (no) for abnormality of clinical significance for the purpose of this study. If 1 (yes) is answered, specify the abnormality.

8.5 Medication History (Screening Visit)

Circle 1 (never taken), 2 (currently taking), 3 (previously took) or 4 (don't know) for each of the medications listed.

8.6 Baseline Drug Kit Sticker (Baseline Visit)

Attach the Baseline Visit drug kit sticker in the space provided on the form.

8.7 Inclusion/Exclusion Criteria (Baseline Visit)

Each individual Inclusion/Exclusion Criteria must be answered.

Inclusion Criteria:
Circle 1 (yes), 2 (no), or 4 (n/a) for each of the questions.

Note: All answers must be yes or n/a to be eligible for the study.

Exclusion Criteria:
Circle 1 (yes), 2 (no), or 4 (n/a) for each of the questions.

Note: All answers must be no or n/a to be eligible for the study.

Inclusion/Exclusion Criteria Summary:
Circle 1 (yes) or 2 (no) for patient fulfilling all inclusion/exclusion criteria.

Note: If 1 (yes) is circled, fax the form to Resa Jeche, the Study Coordinator at the Mayo Clinic (Fax #: 507-284-3923) AND Reina Nakamura, the Study Coordinator (Fax #: 212-628-3648).

*8.8 **Brief Physical Exam** (Baseline, Visit1, Visit 2, Unscheduled, Early Termination)*

Record weight (indicating kg or lb by checking the box), height (checking in or cm), temperature (checking °F or °C), pulse rate, and systolic and diastolic BP. Also answer yes or no for blood and urine samples sent to Lab.

Circle either 1 (normal) or 2 (abnormal) for each of the physical exam items. If 2 (abnormal) is circled for any items, specify the abnormality.

Answer 1 (yes) or 2 (no) for abnormality of clinical significance for the purpose of this study. If 1 (yes) is answered, specify the abnormality.

*8.9 **Nicotine Use** (Baseline Visit)*

Circle 1 (yes) or 2 (no) for smoked at least 100 cigarettes. If 2 (no) is circled, then skip to the other current nicotine use section questions.

Circle 1 (1-10), 2 (11-20), 3 (21-40), 4 (more than 40), 8 (don't know) for cigarettes smoked per day.

Record the total number of years smoked cigarettes.

Circle 1 (yes) or 2 (no) for smoke cigarettes now. If 2 (no) is circled, skip to the other current nicotine use section questions.

Circle 1 (1-10), 2 (11-20), 3 (21-40), 4 (more than 40), 8 (don't know) for cigarettes currently smoke per day.

Other Current Nicotine Use:

Circle 1 (yes) or 2 (no) for questions about nicotine gum, nicotine patch, and other nicotine use. Specify for other forms of nicotine.

Note: Other possible forms of nicotine use are: pipe tobacco, chewing tobacco, nicotine gum, nicotine patches, nicotine inhalers etc.

*8.10 **CDAI** (Baseline, Visit1, Visit 2, Unscheduled, Early Termination)*

This form is self -explanatory. If you do not have experience with using the CDAI and have questions, please contact the Study Coordinator.

Use the Patient Diary to record the number of liquid or very soft stools each day, abdominal pain rating, and general well being (Questions 1, 2, and 3).

For Question 7: Hematocrit % value, use the appropriate box according to whether the patient is male or female.

Calculate the score by adding the subtotal numbers. Be sure to double-check the calculations.

Note: If Visit 1 or Visit 2 CDAI score is 100 points above the Baseline CDAI score, then the patient must be terminated from the study.

8.11 Quality of Life (IBDQ) (Baseline, Visit 1, Visit 2, Early Termination)

This form is designed by be completed by the patient. Remind the patient that the questionnaire is designed to find out how he/she has been feeling during the last 2 weeks. The patient should be instructed to answer each question by circling only one number. Because of the carbons, make sure the form is completed one page at a time (not stacked on top of each other). Check to make sure each question is answered.

8.12 Visit 1 Drug Kit Sticker (Visit 1)

Attach the Visit 1 drug kit sticker in the space provided on the form.

8.13 Prohibited Medications (Visit 1, Visit 2, Unscheduled)

Circle 1 (yes) or 2 (no) for each question about prohibited medications since the last study visit.
Note: If 1 (yes) is circled for any of the questions, the patient should be terminated from the study. Be sure to complete a Study Termination Form in the Early Termination Visit tab.

8.14 Visit Pill Counts (Visit 1, Visit 2, Early Termination)

The patient should be instructed to bring their remaining pills to each and every visit.

Count and record the number of pills left over in the returned yellow and blue bottles separately.

Circle the number (0, 1, 2, or 3) of yellow and blue bottles returned.

Circle 1 (yes) or 2 (no) for next drug kit given to patient.

8.15 Study Termination (All Visits)

The form should be completed at the patient's last visit.

Record the termination date.

Circle one number for the main reason for termination. Record only ONE REASON for termination. If more than one reason for termination applies, circle the primary reason for termination.

Note: Circle 1 if the study was completed normally and not an early termination.

8.16 Concomitant Medication Log (All Visits)

Record all drugs (except the study drug) the patient takes during the study.

For each drug, complete the name, route (PO, IV, etc.), daily dose and frequency, start and stop dates, and indication.

Note: For Med #, please leave blank. The Study Coordinator will code this number.

Note: For Canadian sites, please also include the generic name (trade names in Canada & the U.S. do not always match).

- One Concomitant Medication Log form may contain information over several visits. You should complete the medication log each visit, though, and send in the top white original and 2nd yellow copy form at the patient's last visit.
- At the time of the Screening Visit, record all other medications the patient is taking.
- At each visit, question the patient to see if any new medication(s) are being taken since the last visit or if a previously recorded medication has had a dose change since the last visit.
- If the patient is taking a new medication since the last visit, record the information on a new line.
- If a previous drug has had a dose change, record the last date of the old dose under Stop Date for the previous drug and then go to the next free line and record the Start Date (and other requested data) of the drug at the new dose.
- Route: Route the medication gets delivered, i.e. oral (PO), intravenous (IV) injection, etc.
- Daily Dose and Frequency: Record how much (dose) and how often (frequency) a patient is taking a medication.
- Start and Stop Dates: Record the start and stop dates of each medication at each dosing level.
- Indication: Record the reason why the patient is taking the medication.

Submit the completed form at the end of the study.

8.17 Adverse Events (Baseline, Visit 1, Visit 2, Unscheduled, Early Termination)

The Investigator will report any observed adverse events, as well as those reported by the patient. Any questioning of the patients by the Investigator and staff should be of a general nature and should not prompt the patients to report symptoms.

As defined in the protocol: an adverse event is any undesirable clinical experience occurring to a patient during the clinical study whether or not the AE is considered related to the investigational product. An undesirable experience is any experience that is not related to the condition that qualified the patient for participation in the study. Undesirable experiences include exacerbations of pre-existing conditions. An exacerbation of a condition is when the condition that was present prior to the start of the study occurs more frequently or with greater severity during the study.

Record all adverse events during the study. For each AE, complete the name, date of onset, resolution, date of resolution, duration (circle secs, mins, or hours), relationship to study Med, action taken, withdrawn and whether serious. For serious AEs, also complete the Serious Adverse Event form.
Note: For AE #, please leave blank. The Study Coordinator will code this number.
One Adverse Events form may contain information over several visits. Be sure to review all continuing adverse experiences at every visit. Send in the top white original and 2nd yellow copy form at the patient's last visit.

- Record the name of the Adverse Event, using 1 line for each AE.
- **Date of Onset:** This data is REQUIRED
- **Resolution:** write 1 (Resolved) or 2 (Unresolved) or 3 (Fatal). This data is REQUIRED.
- **Date of Resolution:** This data is only required when the resolution status is 1 (Resolved) or 3 (Fatal), if the Resolution status is 2 (Unresolved) then this data field is skipped.
- **Duration:** This data is only required to be completed when the duration is less then 24 hours. Write the duration of the event and circle the appropriate unit of time.
- **Relation to Study Medication:** Record 1 (unrelated), 2 (unlikely), 3 (possible), 4 (probable) or 5 (definite). This data is REQUIRED.
- **Action Taken:** Write 0 (none), 1 (reduced), 2 (interrupted) or 3 (discontinued). This data is REQUIRED.
- **Withdrawn from study due to AE:** Write 1 (no) or 2 (yes). This data is REQUIRED.
- **Serious:** Write 1 (no) or 2(yes). This data is REQUIRED.

8.18 Serious Adverse Events (Baseline, Visit 1, Visit 2, Unscheduled, Early Termination)

All serious adverse events should be reported immediately by faxing both Reina Nakamura, the Study Coordinator, and Resa Jeche at the Mayo Clinic. The form should also be mailed to Reina. Record all serious adverse events on this form. There should be no missing data. Double-check that all the questions have been answered and that the form is signed and dated by the Principal Investigator.

As defined in the protocol, a serious adverse event is any AE that:

- Results in death.
- Is life threatening. Note: "life threatening" refers to any AE that, as it occurs, puts the patient at immediate risk of death. It does not refer to an AE that hypothetically might have caused death if it were more severe.
- Results in hospitalization or prolongation of current hospitalization (not including hospitalization for a pre-existing condition that has not increased in severity or frequency from the patient's underlying medical condition prior to entry into the study.
- Results in persistent or significant disability/incapacity.
- Is a congenital anomaly/birth defect.

- Is judged to be medically significant. Note: A medically significant AE is a medical event that may not be immediately life threatening or result in death or hospitalization but may jeopardize the patient or require intervention to prevent one of the outcomes listed above.

*8.19 **Adverse Events Comments Page** (Baseline, Visit 1, Visit 2, Unscheduled, Early Termination)*

This form is provided to make additional notes or comments to clarify information about adverse events.

*8.20 **Comments Page** (All Visits)*

This form is provided to make additional notes or comments to clarify information collected on other forms during the study.

*8.21 **Patient Diary** (Screening, Baseline, Visit 1, Visit 2)*

This form should be given to the patient at the Screening Visit. Additional Patient Diary forms should be given to the patient at the Baseline and Visit 1 visits. Instruct the patient to record the month, day, and year, the number of liquid or very soft stools. The patient should also rate their general well- being and abdominal pain (by circling one number). Emphasize the importance of completing the Diary form every day throughout the study- the answers will be used to calculate the CDAI at the next visit. Remind the patient to bring the completed form with them to the next study visit.

Although we know when the study medication is dispensed, there is a potential problem of knowing the exact date the patient begins study medication. Therefore:

It is very important that the patient record the date study drug was started on the first page of the Patient Diary and that the form is mailed to Reina.

9.0 Case Report Forms: Correcting Study Data After Submitted

9.1 Correcting Case Report Form Data after Submitted to Study Coordinator

To make changes to Case Report Forms (CRFs) before data has been sent to the Study Coordinator, mark through the data that is incorrect and write-in the correct data. Initial and date corrections out to the side of the entry.

If corrected or additional study data is made to the Case Report Forms after forms have been submitted to the Study Coordinator, photocopy your copy, and in the top right hand corner of the photocopy write the date of the correction and the words "Corrected Data" and initial and date. The corrected copy should be mailed to Reina Nakamura, the Study Coordinator. A copy of the corrected form should also be kept in the study notebook with the original CRF.

9.2 Queries

Prior to data entry, the case report forms (CRFs) will be reviewed by the Study Coordinator (Reina). Incomplete forms will be sent back to the sites to complete. The data from completed CRFs will be entered by the Data Management Center at the University of North Carolina. Edit checks will be performed on the data and queries will be generated when there are discrepancies in the data. The query forms will be sent to the Study Coordinator and sent back to the sites when the errors cannot be resolved. Incomplete and inconsistent data will generate queries. For example, if a patient has an abdominal mass coded on the CDAI form (Question 6), then Abdomen should be coded as abnormal on the Brief Physical Exam form (Question 2). Query forms should be reviewed and corrected as soon as possible and returned to the Study Coordinator.

TABLE A: SCHEDULE OF EVENTS

Procedure	**Screening**	**Baseline**	**Day 1 - 7**	**Visit 1 (Wk 3)**	**Visit 2 (Wk 6)**
CDAI questions collection (pts to complete)	X	X		X	X
Physician CDAI completion		X		X	X
Informed Consent	X				
Personal/Demographics	X				
Medical History	X				
Concomitant Medication	X	X		X	X
Physical Examination	X			X	X
Clinical Laboratory Tests	X			X	X
Pregnancy Test	X				X
Urinalysis	X				X
IBDQ		X		X	X
Dispense Study Medication				X	
Side Effects Monitoring		X		X	X
Compliance				X	X
Return to Receive Study Medication (or arrange for receipt by mail)			X		